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CONCEPTS ON THE VERGE OF TRANSLATION

Integrating Noninvasive Absolute Flow, Coronary Flow Reserve, and Ischemic Thresholds Into a Comprehensive Map of Physiological Severity

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Noninvasive, absolute myocardial perfusion and coronary flow reserve (CFR) can be imaged by many techniques. However, such data must be interpreted for clinical application regardless of its source. Currently, no guide exists for physiological integration. Therefore, we propose 2-dimensional scatter plots of stress flow and CFR with superimposed thresholds for normal flow, reduced flow without ischemia, definite ischemia, and transmural infarction to allow for automatic and objective classification. Application of this schema to 1,500 studies demonstrates that flow capacity relates inversely to risk factors and atherosclerotic burden. Interpreting stress flow to make clinical decisions requires rest flow or CFR for broad application to all patients. Although relative uptake images alone are adequate for some patients, it can either under- or over-estimate flow capacity in many persons. Our standardized framework could prompt future studies leading to a trial of revascularization guided by absolute flow measurements. (J Am Coll Cardiol Img 2012;5:430–40) © 2012 by the American College of Cardiology Foundation

Noninvasive myocardial perfusion in units of flow per myocardial mass (cc/min/g) and myocardial or coronary flow reserve (CFR) can be imaged by many techniques: positron emission tomography (PET), magnetic resonance imaging, myocardial contrast echocardiography, and contrast computed tomography (CT). However, such data must be interpreted for clinical application regardless of its source. Typically, the clinical question focuses on the severity and size of myocardial ischemia as the basis for identifying the subset of patients in whom invasive angiography and mechanical revascularization will augment the benefit from optimal medical therapy.

Translating quantitative, absolute flow data into a clinical decision must integrate a vast amount of information. A cardiac PET study from our institution produces relative rest and stress uptake at 21 short-axis slices, each of which has 64 radial pixels, each with a corresponding rest and stress flow (in cc/min/g) and their ratio CFR for a total of 6,720 data points. While visual assessment of relative uptake, absolute flow, and CFR remains the foundation of image interpretation, true quantitative analysis offers advantages of automation, reproducibility, and objectivity. However, currently no guide exists for physiological integration of noninvasive myocardial perfusion and CFR.

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Therefore, we present a framework for the physiological integration of absolute flow and CFR data and apply it to 1,500 sequential cases. Although all cases were acquired using cardiac PET, the framework and its application hold for any imaging modality. First, we note that since only 2 parameters from rest flow, stress flow, and CFR are independent, a 2-dimensional scatter plot uniquely captures the data. Second, we incorporate flow and CFR thresholds from our earlier publications documenting their range from young, asymptomatic normal volunteers (1) to low-flow limits for myocardial ischemia (2). Finally, we classify and describe major clinical groupings as management guides and discuss representative examples.

Myocardial perfusion by PET. A total of 1,500 cardiac PET studies were performed in 1,249 unique subjects between April 2007 and June 2011. Subjects included both young, asymptomatic normal volunteers (1) and clinical patients representing the entire spectrum of cardiac atherosclerotic disease: assessment or follow-up of known coronary artery disease (CAD), second opinions on revascularization procedures, prior positive stress tests, coronary calcification by CT, chest pain or other symptoms, or risk factors. Our PET acquisition and processing protocol with absolute flow quantification is described in previous publications (1,2).

In brief, rest then stress perfusion images were acquired using Rb-82 on a PET scanner with hybrid 16-slice CT for attenuation correction, shifted as needed for coregistration. An optional third scan was gated to estimate ejection fraction (EF) in clinical patients but not research volunteers. Intravenous dipyridamole produced hyperemia before stress imaging. Image processing converted raw, unrotated 3-dimensional data into standard 2-dimensional topographic maps reflective of left ventricular (LV) anatomy. Quantitative flow used a simple, integrative model validated experimentally (3). Demographic information, cardiac history, risk factors, hemodynamics, and presence of dipyridamole-induced angina and ST-segment deviation were recorded.

Quantitative relative uptake endpoints did not use 4 basal slices because of low counts in the membranous interventricular septum. Two apical slices were not used for quantitative analysis of relative uptake images because of potential partial volume errors caused by partial thickness slices through the LV apex and apical motion. Combined size and severity of relative perfusion defects was quantified by 2 metrics: first, the percent of the whole topographic image with relative activity <60% of maximum activity (100%), which is >6 SDs below the lowest quadrant mean activity in normal patients (1); and second, the value in the quadrant with the lowest average relative uptake (minimum quadrant average). An established index quantified relative uptake homogeneity.

Statistical analyses were performed using R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as mean ± SD, or median (interquartile range) for non-normal distributions, and were compared among groups using analysis of variance (or Kruskal-Wallis test for non-normal distributions). Visual analysis of quantile-quantile plots determined if a variable was approximately normal. Coefficient of variation (COV) was defined as the standard deviation as a percentage of the mean. Frequency variables are expressed as number (percent) and were compared using a chi-square test or Fisher exact test. Association between paired, continuous variables was summarized using the Pearson correlation coefficient. Applicable tests were 2-tailed, and $p < 0.05$ was considered statistically significant. Analysis was performed on a case basis rather than on a subject basis to reflect clinical practice, where repeat scans in the same patient might be performed for changes in clinical status or management follow-up.

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve
CAD = coronary artery disease
CFR = coronary flow reserve
COV = coefficient of variation
CT = computed tomography
EF = ejection fraction
LAD = left anterior descending artery
LV = left ventricular
PET = positron emission tomography
PRP = pressure-rate product

Integrating absolute flow with its thresholds. CFR equals the ratio of absolute stress flow to absolute rest flow. Therefore, only 2 of these 3 variables are independent. While any of 3 possible combinations could fully represent the data, we chose CFR (unitless) and absolute stress flow (in cc/min/g) for scatter plot axes because of literature on their thresholds for ischemia. Figure 1 depicts an annotated conceptual scatter plot without any data, whose components are described next.

Straight lines through the origin represent constant values of absolute rest flow (thick dashed lines in Fig. 1, denoting 0.2, 0.5, 1, and 2 cc/min/g). Once rest flow falls too low chronically, myocardial perfusion fails to meet metabolic need, and either infarction or hibernation occurs. Therefore, the lowest rest flow boundary on the scatter plot identifies predominantly transmural myocardial scar (colored black in Fig. 1), observed to be >3 standard deviations below the average rest flow in young, normal volunteers (1). Conversely, the wide

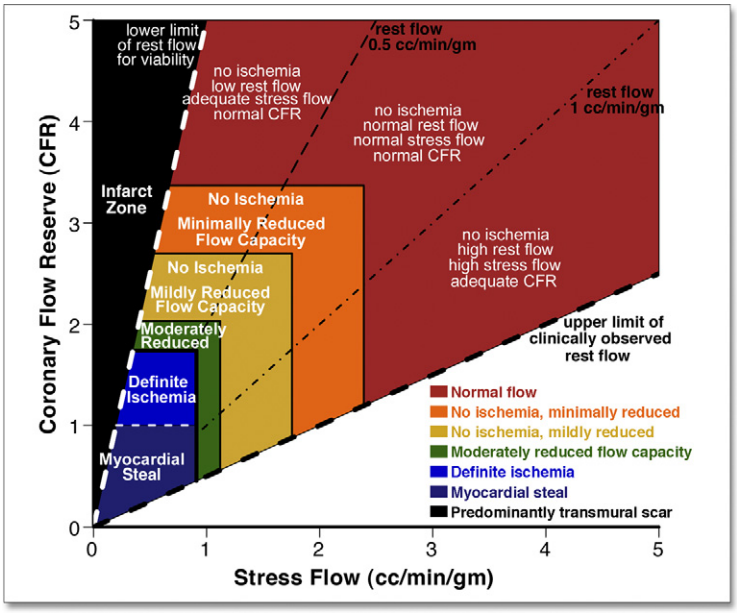

Figure 1. Scatter Plot of CFR Versus Absolute Stress Flow

As coronary flow reserve (CFR) equals stress flow divided by rest flow, a 2-dimensional plot completely determines all 3 variables. See text for further details.

spectrum of rest flow typically stays below an upper bound for the observed clinical range of resting hemodynamics and myocardial contraction. Therefore, almost no observed data exceed the upper rest flow boundary on the scatter plot (colored white). The normal range of rest flow falls between these 2 boundaries and contains the majority of data (thick dashed lines denoting 0.5 and 1 cc/min/g).

Horizontal lines represent constant values of CFR (solid horizontal lines). As CFR falls, eventually flow reserve becomes insufficient to avoid ischemia during hyperemia. Although this transition is obviously graded and not abrupt, binary discriminatory CFR thresholds for ischemia have been documented (2). Therefore, low CFR boundaries on the scatter plot identify definite myocardial ischemia (1.74, colored dark blue) as well as moderately reduced CFR that can produce some manifestations of ischemia (2.03, colored dark green). Once CFR falls below 1, coronary or myocardial steal occurs denoting that "hyperemic" flow is actually less than basal flow (colored dark purple).

Similarly, vertical lines represent constant values of absolute stress flow in cc/min/g (solid vertical lines). As with falling CFR, reduced stress flow eventually becomes insufficient to avoid ischemia during hyperemia, and binary low-flow thresholds for ischemia exist along this continuum (2). Therefore, low stress flow boundaries on the scatter plot identify definite myocardial ischemia (0.91 cc/min/g, colored dark blue) as well as moderately reduced hyperemic flow that can produce some manifestations of ischemia (1.12 cc/min/g, colored dark green).

Typical ranges for both CFR and stress flow have been described in young, asymptomatic normal volunteers (1). Normal CFR and stress flow limits on the scatter plot drawn 1 standard deviation below the mean (CFR 3.37, stress flow 2.39 cc/min/g) identify regions of perfusion typically seen in this nonclinical cohort (colored red). The majority of clinical patients demonstrates perfusion between the normal limit and the low threshold for ischemia. This area has been divided into 2 (by CFR of 2.70, stress flow 1.76 cc/min/g) to distinguish minimally reduced perfusion but no ischemia (colored orange) from mildly reduced perfusion but no ischemia (colored yellow).

Each data point plotted on Figure 1 can be quickly interpreted by its color as representing a region of myocardium with a normal, reduced, ischemic, or infarct flow capacity. When data from the entire left ventricle are plotted, each quadrant can be summarized by its mean and interquartile range. The number of data points in each colored region provides an objective assessment of ischemic burden, infarct size, and overall and regional flow capacity. The scatter among the pixels is responsible

for relative uptake perfusion defects: great scatter will produce a relative uptake defect even if all flows are nonischemic, whereas minimal scatter will produce uniform relative uptake even if all flows are severely reduced.

If each LV region is colored by where its data falls on the scatter plot, then a new map can be produced integrating spatial localization with interpreted flow capacity combining maximum absolute flow and CFR. Nontransmural infarction is identified from the relative uptake images when both rest and stress fall below 6 standard deviations of the lowest quadrant average in normal volunteers (60% at rest, 60% during hyperemia) (1) to produce a contiguous region at least 5% of the entire left ventricle.

Patient example. Figure 2 displays comprehensive data from a single patient, including relative uptake maps, absolute flow and CFR maps, scatter plot data as in Figure 1, coronary flow map that combines the scatter plot color for each pixel with the typical anatomic distribution of the major epicardial arteries based on angiogram-PET correlations, and key data from the invasive angiogram.

Relative uptake images show a small, distal septal nontransmural myocardial infarction (2% of left ventricle <60% of maximum at rest) with a large stress-induced defect (20% of left ventricle <60% at stress). Absolute flow images show a large area of reduced stress flow (50% of the left ventricle <2 cc/min/g) and CFR (18% of the left ventricle with CFR <2) in the septal and anterior quadrants. The scatter plot of CFR versus absolute stress flow as in Figure 1 demonstrates 8% of the left ventricle with moderately reduced flow capacity and 6% with definite ischemia. The coronary flow map with superimposed and labeled arterial distributions localizes ischemic regions to the second diagonal branch (D2) with a nontransmural scar (hashed grid) in the mid-to-distal septal quadrant. Invasive angiography demonstrates diffuse but nonobstructive disease in the left anterior descending (LAD) artery with a distal fractional flow reserve of 0.83 (orange arrowhead) during intravenous adenosine infusion and no focal gradient on pullback. However, the saphenous vein graft (upper right inset in solid white box) to D2 is closed, and D2 (large, dark blue arrowheads) fills by collaterals (small red arrows) from the LAD (lower right inset in dashed white box). Dual-headed, solid arrows compare regions on the flow map to corresponding regions on the angiogram.

The coronary flow map in Figure 2 allows effortless distinction between a distal septal nontransmural myocardial infarction and occlusion of the saphenous vein graft to a diagonal branch, while the

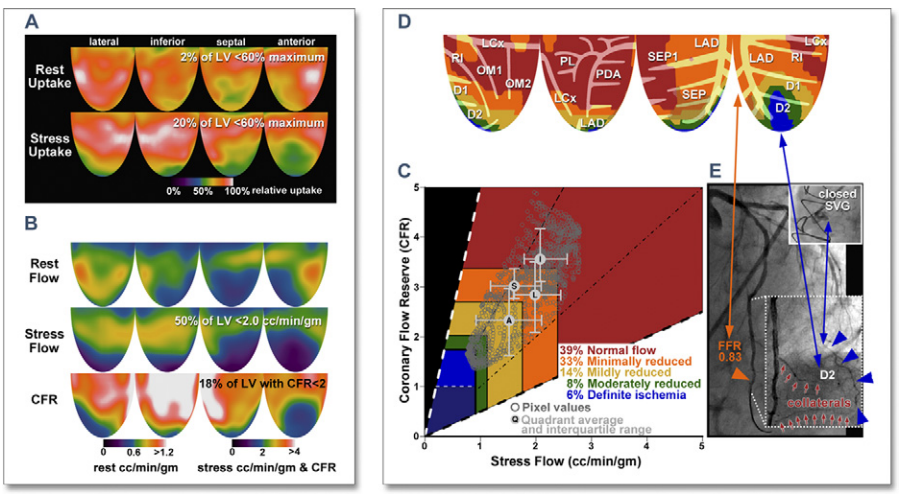

Figure 2. Clinical Example With Complete Data

A 72-year-old woman with extensive prior mechanical revascularization including bypass surgery is shown. **(A)** Relative uptake images. **(B)** Absolute flow images. **(C)** Scatter plot of CFR versus absolute stress flow as in Figure 1. **(D)** Coronary flow map with superimposed and labeled arterial distributions. Each pixel from **C** is colored from its location on the scatter plot. **(E)** Invasive angiography of the left anterior descending artery (LAD) and its now-occluded vein graft to the second diagonal. See text for further details. D1 = first diagonal branch; D2 = second diagonal branch; FFR = fractional flow reserve; LCx = left circumflex; LV = left ventricle; OM1 = first obtuse marginal branch; OM2 = second obtuse marginal branch; PDA = posterior descending artery; PL = posterolateral left ventricular branch; RI = ramus intermedius; SEP1 = first septal perforator; SEP = other septal perforators; SVG = saphenous vein graft.

relative uptake and absolute flow maps make this inference more difficult. Fractional flow reserve confirmed preserved flow capacity in the distribution of the LAD itself, while collaterals sufficient to avoid myocardial steal during hyperemia supply the D2 branch whose vein graft had occluded.

Necessity of considering rest flow. Figure 3 contrasts 2 cases with nearly identical but reduced absolute stress flow (average for whole left ventricle in cc/min/g: 1.18 for patient A, 1.24 for patient B) in which rest flow, and hence CFR and the clinical interpretation, varies markedly. Low flow at rest, as due to sufficient medical management with beta-blockade, can pair with reduced stress flow to result in adequate or even normal CFR and no ischemia. High flow at rest, however, as due to uncontrolled blood pressure and heart rate, can couple with reduced stress flow to bring CFR and, hence, flow capacity to ischemic levels.

Average whole LV rest flow in all studies was 0.70 ± 0.20 cc/min/g (range 0.33 to 1.82 cc/min/g) with a COV of 28%. The correlation between baseline pressure-rate product (PRP) and rest flow was r = 0.63, implying that PRP accounts for 40% of the variation in rest flow. Dividing rest flow by baseline PRP and multiplying by 10,000 produces an adjusted rest flow for our studies of 0.99 ± 0.22 (range 0.48 to 2.06) with a COV of 22%. Average whole LV stress flow was 2.06 ± 0.71 cc/min/g (range 0.30 to 5.91 cc/min/g) with a COV of 34%. The correlation between hyperemic PRP and stress flow was r = 0.50, implying that PRP accounts for 27% of the variation in stress flow.

Taking the worst (minimum) quadrant average stress flow and CFR and using boundaries of stress flow <0.91 cc/min/g ("ischemic" hyperemic flow) and CFR <1.74 ("ischemic" CFR) divides our 1,500 cases into 4 groups, to which our previous criteria (2) for definite ischemia (stress-induced PET defect with either significant ST-segment depression and/or severe angina) can be applied: 1,271 scans have both preserved CFR and stress flow, of which 15 (1%) show definite ischemia; 112 have both ischemic CFR and stress flow, of which 53 (47%) show definite ischemia; 92 scans have ischemic CFR but preserved stress flow, of which 13 (14%) show definite ischemia; and 25 scans have preserved CFR but ischemic stress flow, of which 2

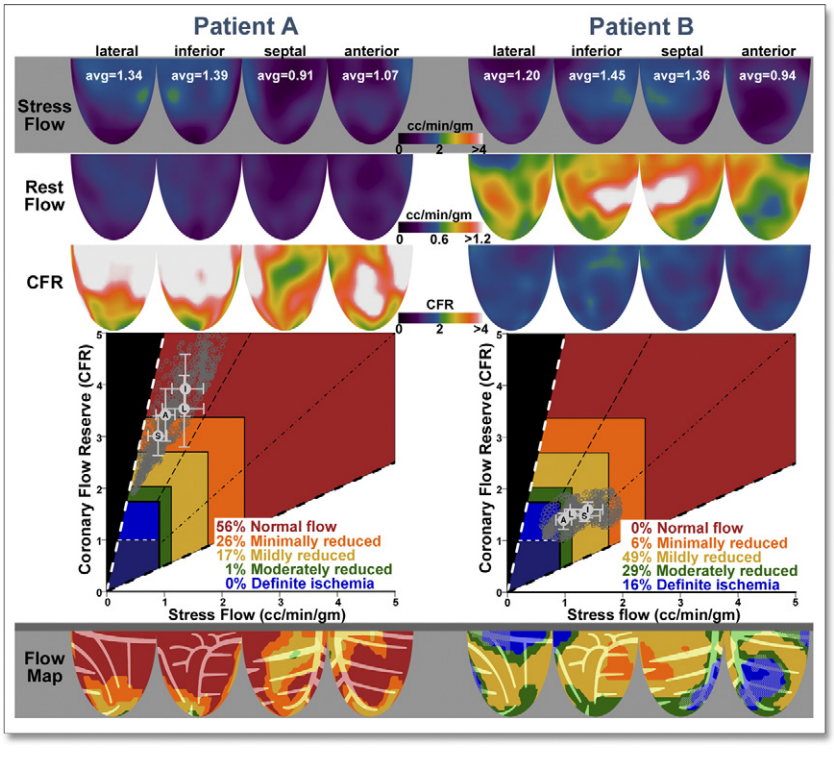

Figure 3. Necessity of Considering Rest Flow

Each column displays data for an individual patient: stress flow (**first row**), rest flow (**second row**), coronary flow reserve (CFR) (**third row**), CFR versus absolute stress flow scatter plot as in Figure 1, and flow map. **Gray boxes** contrast similar absolute stress flows but dramatically different flow maps due to differences in rest flow.

(8%) show definite ischemia. The vast majority (92%) of cases have concordant stress flow and CFR. However, among patients with ischemic stress flow, 18% have preserved CFR. Additionally, among patients with preserved stress flow, 7% have ischemic CFR. Definite ischemia as defined previously (2) is similar in patients with discordant CFR and stress flow (Fisher p = 0.52), although small numbers limit generalizability.

Representative groupings. Cardiac PET scans were objectively classified into 6 unique groups, each corresponding to a major color in Figure 1 defined as follows: 1) red color, volunteers—all young, asymptomatic, normal volunteers as has been previously reported (1) plus an additional 9 scans in 5 volunteers completed after that publication; 2) red color, clinical patients—clinical patients with normal flow capacity, defined as at least 80% of the left ventricle with normal flow (red zone of Fig. 1) and <1% in the moderately reduced, definitely ischemic, or transmural infarct areas (green, blue, purple, and black zones); 3) orange color—patients with minimally reduced flow capacity, defined as a larger normal or minimally reduced territory (red and orange) than mildly reduced territory (yellow) and <10% in the ischemic or transmural infarct areas; 4) yellow color—patients with mildly reduced flow capacity, defined as a larger minimally or mildly reduced territory (orange and yellow) than normal territory (red zone) and <10% in the ischemic or transmural infarct areas; 5) green, blue, purple, black colors, some ischemia—patients with at least 10% LV burden of moderately reduced flow capacity (green), definite ischemia (blue or purple), or transmural infarct (black) with <10% of the LV with a relative stress-induced defect <60% of maximum, representing patients with either large transmural infarcts or small-to-moderate ischemia, as might be appropriate for initial medical management; and 6) green, blue, purple, black colors, large ischemia—as for group 5 but ≥10% of the left ventricle with a relative stress-induced defect <60% of maximum, representing patients with an ischemic burden which would likely benefit from mechanical revascularization.

Table 1 gives demographic, clinical, and PET scan characteristics by flow grouping. Risk factor burden, clinical symptoms, and manifest atherosclerosis relate inversely and significantly to flow capacity. Figure 4 demonstrates both a representative topographic flow capacity map of the LV and the scatter plot for each of the major groupings (normal groups 1 and 2, minimally reduced group 3, mildly reduced group 4, and ischemic burden groups 5 and 6).

Figure 5 presents 2 cases each from groups 6 to 4. For each group, the cases emphasize the discordance that can be seen between relative uptake and flow capacity. Relative rest uptake images are not shown but were practically normal and do not change the clinical interpretation, except as noted for subfigure A. Shown in A1, left, is a 54-year-old man with debilitating angina. Resting relative uptake showed the anterior defect was partially due to a nontransmural infarct; angiography confirmed a totally occluded mid-LAD lesion. Shown in A2, right, is a 64-year-old man who became profoundly ischemic and hypotensive during dipyridamole hyperemia. Resting relative uptake showed the basal inferolateral defect to be mixed viable tissue and nontransmural infarct; angiography demonstrated severe left main and triple-vessel disease. Shown in B1, left, is a 58-year-old woman with essentially normal stress uptake but globally depressed flow with 29% of the left ventricle demonstrating moderately reduced flow capacity or definite ischemia. In B2, right, is a 66-year-old man with large stress defect (47% of the left ventricle <60% of maximum) but moderately reduced flow globally with only small, scattered areas of definite ischemia. In C1, left, is an 83-year-old man with normal stress uptake but moderately reduced flow globally (whole left ventricle average CFR 2.26). In C2, right, is an 85-year-old woman with large stress defect due to nonischemic but differential flow capacity between the lateral (average CFR 1.29) and septal (average CFR 1.83) quadrants.

Figure 6 presents 2 cases each from groups 3 to 1 as in Figure 5. A1, left, shows a 76-year-old man with completely normal relative uptake but mildly reduced flow capacity diffusely (whole left ventricle average stress flow 1.71 cc/min/g, CFR 2.87). A_2, right, shows a 57-year-old man with extensive, prior mechanical revascularization where above average flow capacity in the lateral and inferior quadrants (average CFR 3.71) produces a relative uptake defect in the septal and anterior quadrants (24% of the left ventricle <60% of maximum) despite adequate flow capacity (worst CFR 1.98, average septal CFR 2.99). B1, left, shows a 76-year-old man with dense coronary calcium in all arteries, typical resting flow (whole left ventricle average 0.62 cc/min/g), but CFR as seen in young, healthy, normal volunteers (whole left ventricle average 4.11). B2, right, shows a 75-year-old man with relative uptake defect in wrap-around mid-LAD distribution but normal

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Table 1. Clinical Features by Flow Group

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	p Value
Number of studies	241 (16)	258 (17)	610 (41)	108 (7)	163 (11)	120 (8)	NA
Age, yrs	28 ± 5	56 ± 11	63 ± 10	65 ± 10	68 ± 10	67 ± 10	<0.001
Male	181 (75)	195 (76)	466 (76)	82 (76)	138 (85)	102 (85)	0.06
Diabetes mellitus	0 (0)	18 (7)	90 (15)	21 (19)	53 (33)	27 (22)	<0.001
Current or past tobacco use	27 (11)	86 (33)	271 (44)	43 (40)	95 (58)	51 (42)	<0.001
Hypertension	0 (0)	126 (49)	381 (62)	75 (69)	116 (71)	83 (69)	<0.001
Dyslipidemia	40 (17)	222 (86)	571 (94)	104 (96)	157 (96)	112 (93)	<0.001
Family history of CAD	110 (46)	206 (80)	452 (74)	76 (70)	118 (72)	83 (69)	<0.001
Recent clinical angina	0 (0)	6 (2)	29 (5)	5 (5)	16 (10)	31 (26)	<0.001
Prior PCI or CABG	0 (0)	28 (11)	196 (32)	33 (31)	101 (62)	73 (61)	<0.001
Angina during PET	0 (0)	2 (1)	17 (3)	2 (2)	14 (9)	47 (39)	<0.001
ST-segment depression during PET	0 (0)	6 (2)	23 (4)	4 (4)	12 (7)	48 (40)	<0.001
Ejection fraction, %	NA	72 ± 8	70 ± 9	71 ± 9	66 ± 12	61 ± 11	<0.001
Relative uptake							
Rest <60% of maximum (% of LV)	0 (0–1)	0 (0–2)	0 (0–3)	0 (0–2)	3 (0–11)	3 (1–12)	<0.001
Stress <60% of maximum	0 (0–0)	0 (0–0)	0 (0–3)	0 (0–1)	5 (1–13)	29 (20–39)	<0.001
Rest minimum quadrant average, %	80 (77–81)	78 (75–80)	78 (74–80)	78 (74–80)	74 (67–79)	74 (68–78)	<0.001
Stress minimum quadrant average	82 (80–84)	80 (77–83)	78 (74–81)	78 (75–81)	72 (64–77)	59 (51–64)	<0.001
Rest homogeneity index (no units)	0.49 ± 0.09	0.43 ± 0.10	0.43 ± 0.11	0.43 ± 0.11	0.39 ± 0.11	0.40 ± 0.10	<0.001
Stress homogeneity index	0.60 ± 0.11	0.54 ± 0.13	0.49 ± 0.12	0.47 ± 0.11	0.40 ± 0.09	0.43 ± 0.10	<0.001
Absolute flow, cc/min/g							
Rest whole LV average	0.70 ± 0.15	0.75 ± 0.24	0.72 ± 0.20	0.69 ± 0.16	0.62 ± 0.14	0.64 ± 0.18	<0.001
Stress whole LV average	2.71 ± 0.58	2.78 ± 0.59	1.99 ± 0.34	1.51 ± 0.16	1.18 ± 0.26	1.23 ± 0.37	<0.001
CFR whole LV average	4.02 ± 0.85	3.94 ± 0.77	2.91 ± 0.51	2.26 ± 0.30	1.93 ± 0.40	1.97 ± 0.59	<0.001
Rest minimum quadrant average	0.65 ± 0.14	0.69 ± 0.22	0.65 ± 0.19	0.64 ± 0.15	0.54 ± 0.14	0.56 ± 0.17	<0.001
Stress minimum quadrant average	2.55 ± 0.56	2.58 ± 0.57	1.80 ± 0.35	1.36 ± 0.16	0.97 ± 0.25	0.85 ± 0.32	<0.001
CFR minimum quadrant average	3.79 ± 0.81	3.69 ± 0.73	2.69 ± 0.49	2.10 ± 0.29	1.71 ± 0.35	1.46 ± 0.50	<0.001
Flow interpretation, % of LV							
Normal	99 (87–100)	96 (89–99)	33 (14–59)	0 (0–2)	0 (0–0)	2 (0–15)	<0.001
Minimally reduced	1 (0–12)	4 (1–10)	50 (35–62)	30 (16–39)	5 (1–16)	19 (8–31)	<0.001
Mildly reduced	0 (0–0)	0 (0–0)	10 (3–23)	65 (57–77)	50 (35–67)	28 (17–41)	<0.001
Moderately reduced	0 (0–0)	0 (0–0)	0 (0–0)	3 (1–5)	18 (11–26)	10 (7–16)	<0.001
Definite ischemia	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	10 (4–22)	14 (9–23)	<0.001
Myocardial steal	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	7 (0–19)	<0.001
Largest area of definite ischemia	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	7 (3–19)	22 (10–41)	<0.001
Nontransmural infarct	0 (0)	0 (0)	24 (4)	1 (1)	38 (23)	38 (31)	<0.001
Predominantly transmural infarct	0 (0)	2 (1)	10 (2)	2 (2)	26 (16)	15 (12)	<0.001

Values are n (%), mean ± SD, or n (interquartile range).
CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CFR = coronary flow reserve; LV = left ventricle; NA = not applicable; PCI = percutaneous coronary intervention; PET = positron emission tomography.

flow capacity (whole left ventricle average CFR 4.20). Shown in C1, left, is a 30-year-old healthy volunteer with normal relative uptake but reduced flow capacity due to residual caffeine (serum level 2.6 mg/l). And in C2, right, a 27-year-old healthy volunteer with mildly heterogeneous uptake, likely due to nicotine (metabolite detected in the urine) is shown.

Clinical applicability and future studies. We demonstrate an integrative, physiological framework for interpreting noninvasive absolute flow and CFR data. Its preliminary application in 1,500 sequential cases offers several insights.

Rest flow is necessary to interpret hyperemic flow correctly in a significant minority of cases. As demonstrated in Figure 3, nearly identical stress flow images lead to opposite interpretations when rest flow or CFR is considered. Such discordance occurred in 8% of cases, but performing stress-only imaging would produce discordant positives in 18% of cases and discordant negatives in 7%. The discordance between stress flow and CFR primarily

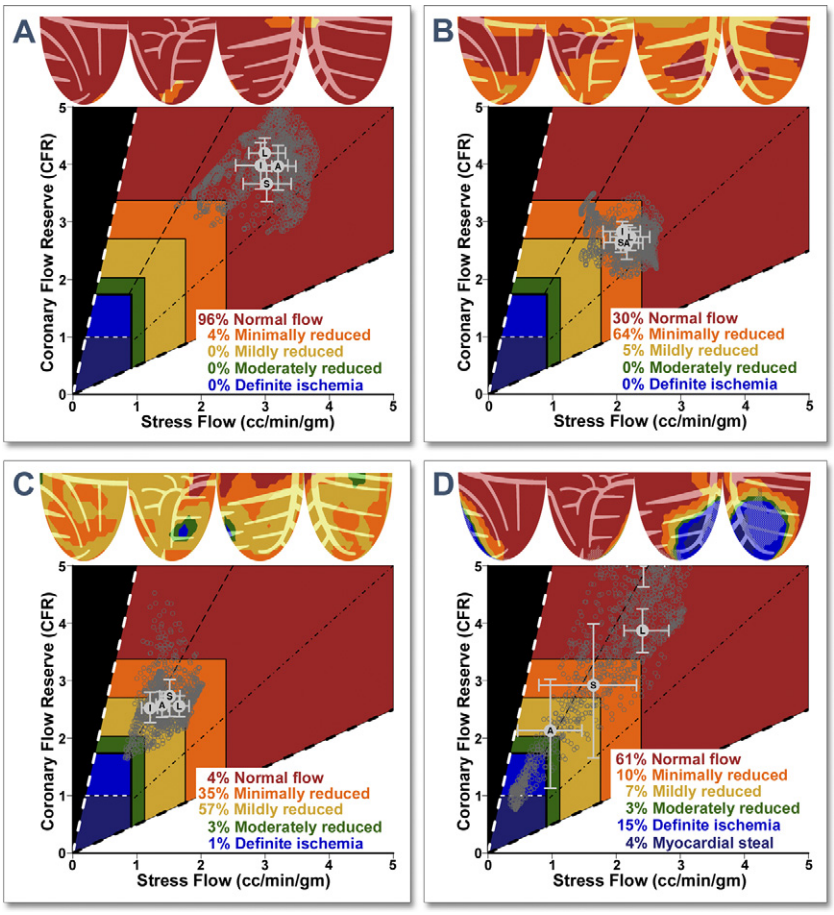

Figure 4. Scatter Plot Examples for Flow Groupings

Each panel demonstrates the flow capacity map (derived from Fig. 1) and corresponding coronary flow reserve (CFR) versus absolute stress flow scatter plot (as in Fig. 1) for typical examples of subjects in each major flow grouping from Table 1. **(A)** Normal volunteer or clinical patient with mostly normal flow (groups 1 and 2). **(B)** Little ischemia with mostly minimally reduced flow (group 3). **(C)** Little ischemia with mostly mildly reduced flow (group 4). **(D)** Large area of moderately reduced flow capacity or definite ischemia (groups 5 and 6).

reflects variable rest flow altered by medications or physiological conditions with corresponding variable clinical consequences. Although further study of these subgroups is necessary, physiology suggests that perhaps only patients with concordantly reduced stress flow and CFR to ischemic levels will benefit from mechanical revascularization. Interestingly, either reduced CFR or stress flow (with the other preserved) appears associated with a similar frequency of definite ischemic manifestations (2).

Considering either CFR or stress flow alone fails to reflect ischemic flow physiology in some patients. These different measures of flow capacity associated with definite ischemia may reflect biological variability of the coronary response to upstream stenosis. For example, with low rest flow and a substantial stenosis, vasodilatory hyperemia may substantially increase coronary artery flow, producing a large pressure gradient, low distal perfusion pressure, and subendocardial ischemia despite CFR above the average ischemic CFR threshold (corresponding to the 18% of patients with ischemic stress flow but preserved CFR). In another case with slightly worse stenosis, vasodilation may maintain resting average transmural flow but with near ischemic subendocardium. Even minimal additional vasodilator stress that barely increases flow (low CFR) causes a disproportionately large stenosis pressure gradient, low perfusion pressure, and severe subendocardial ischemia despite average transmural flow above the average maximum ischemic flow threshold (corresponding to the 7% of patients with preserved stress flow but ischemic CFR).

These 2 examples and our data illustrate several major conceptual points: 1) maximum absolute flow

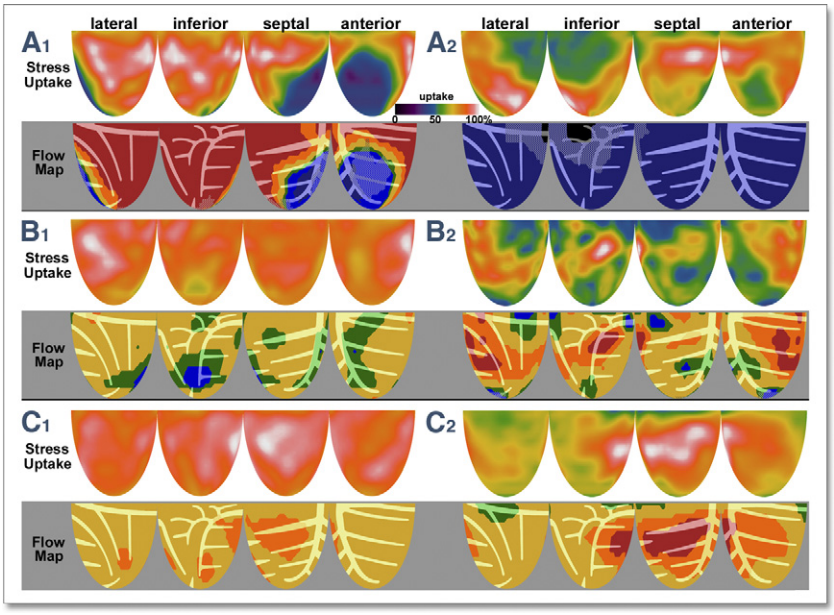

Figure 5. Examples of Moderately and Severely Reduced Flow Capacity

Each subfigure displays 2 contrasting cases in the same flow grouping as in Table 1: A = group 6, B = group 5, C = group 4. Relative stress uptake (rows 1, 3, and 5) appears above matched flow maps (rows 2, 4, and 6) with superimposed arterial distributions (coloring as in Fig. 1). Relative rest uptake images are not shown but were practically normal and do not change the clinical interpretation, except for subfigure A. See text for clinical details.

and CFR accounting for rest flow are both necessary to define low flow thresholds of ischemia for the wide spectrum of clinical patients; 2) profound pressure-flow changes causing ischemia may occur with small or insignificant changes in average PRP or other global measures of demand; and 3) measures of absolute subendocardial perfusion in cc/min/g or the endoepicardial perfusion ratio may provide further insight into these physiological mechanisms of ischemia.

Absolute flow tracks inversely with risk factors, clinical symptoms, and atherosclerotic burden. Table 1 demonstrates that grouping first by flow capacity subsequently orders all other clinical variables. Prior work has demonstrated continuous and graded reductions in stress flow and CFR with risk factor burden (4). By contrast, our current study reverses the order of analysis. When ordered by flow capacity, patients exhibit continuous and graded increases in risk factors and atherosclerotic burden, as in Table 1. Therefore, absolute flow and flow reserve offer integrative assessment of physiological severity of atherosclerosis, as opposed to risk factors that serve as surrogates.

Finally, relative uptake need not mirror flow capacity. Figures 5 and 6 highlight notable cases of discordance between relative myocardial uptake and flow capacity, thereby emphasizing the clinical utility of quantifying absolute flow and coronary flow reserve.

The boundaries in Figure 1 require empiric data for several thresholds: rest flow in transmural myocardial infarction; range of rest flow seen clinically; CFR and absolute stress flow in ischemic myocardium; and CFR and absolute flow in normal subjects free of atherosclerosis. In comparison to our flow and CFR thresholds for ischemia, Table 2 presents results from the literature for the ischemic CFR threshold drawn from a variety of noninvasive and invasive tools in humans. While variation exists due to measurement technique, clinical endpoint, patient population, and biologic heterogeneity, a remarkable consensus can be seen. Therefore, the concepts of Figure 1 appear universal and not overly dependent on a certain method, rendering them appropriate for application to all techniques that can measure absolute flow and CFR.

Several limitations should be kept in mind. Although ischemia occurs when supply cannot satisfy demand, we did not determine the predominately subendocardial reduction (as may occur during vasodilator hyperemia due to disrupted autoregulation) for an "adequate" transmural flow that, however, may reach ischemic levels with increased

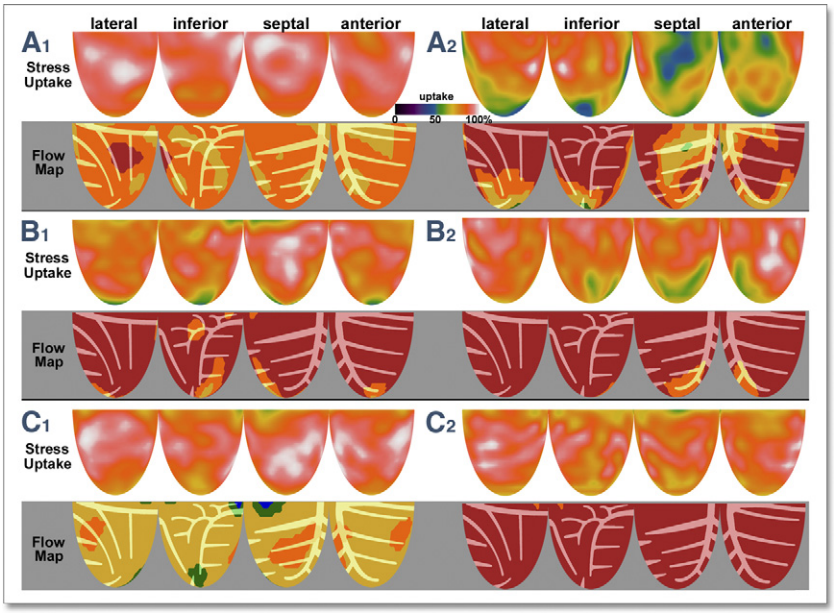

Figure 6. Examples of Normal and Mildly Reduced Flow Capacity

Each subfigure displays 2 contrasting cases in the same flow grouping as in Table 1: A = group 3, B = group 2, C = group 1. Relative stress uptake (rows 1, 3, and 5) appears above matched flow maps (rows 2, 4, and 6) with superimposed arterial distributions (coloring as in Fig. 1). Relative rest uptake images are not shown but were clinically normal and do not change the clinical interpretation. See text for clinical details.

demand (as during exercise stress). Nor could we account for individual factors such as ischemic conditioning or angina perception threshold that introduce biologic variability, as discussed previously (2). Although myocardial PET perfusion is not widely available, all imaging modalities for quantifying absolute myocardial perfusion currently show similar, limited utilization. Additionally, noninvasive flow in humans lacks an obvious gold standard external reference, unlike microsphere or

Table 2. Literature Values for Coronary Flow Reserve Ischemic Thresholds

Author	Journal	Citation	Modality	n	Reference	Cutoff	AUC
Heller	Circulation	1997;96:484		55	SPECT defect	1.7	NA
Chamuleau	J Am Coll Cardiol	2001;37:1316		127	SPECT defect	1.7	0.70
Deychak	Am Heart J	1995;129:219	CFVR	17	SPECT defect	1.8	NA
Verberne	Heart	1999;82:509		37	SPECT defect	1.9	0.85
Danzi	J Am Coll Cardiol	1998;31:526		39	Dipyridamole echocardiography	2.0	NA
Lockie	J Am Coll Cardiol	2011;57:70		42	FFR <0.75	1.58	0.89
Hundley	Circulation	1999;99:3248		30	Cath %DS >70%	1.7	NA
			CMR		Cath %DS ≥70%	1.84	
Costa	J Am Coll Cardiol	2007;50:514		37	FFR ≤0.75	1.97	NA
					Cath %DS ≥50%	2.12	
Vogel	Heart	2009;95:377	MCE	48	Cath %DS ≥50%	1.94	0.93
Peltier	J Am Coll Cardiol	2004;43:257		35	Cath %DS >70%	2.00	NA
Hajjiri	J Am Coll Cardiol Img	2009;2:751	PET	27	Cath %DS ≥70	2.0	0.86
Muzik	J Am Coll Cardiol	1998;31:534		51	Clinically normal group and cath data	2.74	0.91
		Weighted average	**Various**	**545**	**Various**	**1.91**	**0.82**
Johnson	J Am Coll Cardiol Img	2011;4:990	PET	1,674	PET defect, dipyridamole angina/ST	1.74	0.91
					Only 1 of these 3 features	2.03	0.77

AUC = area under the curve; Cath = catheterization; CFVR = invasive coronary flow velocity reserve by Doppler catheter; CMR = cardiac magnetic resonance imaging; %DS = percent diameter stenosis during invasive angiography; MCE = myocardial contrast echocardiography; SPECT = single-photon emission computed tomography; other abbreviations as in Table 1.

flow probe techniques in animal models. Whereas our framework is internally consistent and tracks as expected with risk factors in Table 1, such data do not support a causal relationship other than association of both with coronary atherosclerosis.

Our framework offers an objective, automatic, and quantitative tool for interpreting measurements of absolute flow. Given the large amount of data produced when imaging absolute flow, such a physiological schema is necessary for fast, reproducible interpretation. Key advantages to the CFR versus stress flow scatter plot in Figure 1 are its applicability to any imaging modality, objective limits for ischemia, reduced flow capacity without ischemia, scar and normalcy, and ability to handle both small and large data sets (for example, data from both a single short-axis slice as well as whole LV coverage). The clinical case in Figure 2 highlights the advantages to be gained by an integrated color map.

Future work in this area should lead to a revascularization trial based on noninvasive imaging of absolute flow. Key milestones along this road include clarifying the relationship between noninvasive flow measurements and invasive fractional flow reserve, studying the outcomes of patients with discordant stress flow and CFR classifications, and examining the consistency and reproducibility of flow measurements among imaging modalities and flow models.

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Key Words: absolute flow quantification ■ coronary flow reserve ■ ischemia ■ positron emission tomography.